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# Reduced-Intensity Conditioning followed by Peripheral Blood Stem Cell Transplantation for Adult Patients with High-Risk Acute Lymphoblastic Leukemia

*Anthony S. Stein,[1] Joycelynne M. Palmer,[2] Margaret R. O'Donnell,[1] Neil M. Kogut,[3] Ricardo T. Spielberger,[3] Marilyn L. Slovak,[2] Ni-Chun Tsai,[2] David Senitzer,[2] David S. Snyder,[1] Sandra H. Thomas,[1] Stephen J. Forman[1]*

Acute lymphoblastic leukemia (ALL) with high-risk features has a poor prognosis in adults despite aggressive chemotherapy. Reduced-intensity conditioning (RIC) is a lower toxicity alternative for high-risk patients requiring hematopoietic cell transplantation (HCT); however, it has not been widely used for ALL. We conducted a retrospective study of 24 high-risk adult ALL patients who received an RIC regimen of fludarabine (Flu)/melphalan (Mel) prior to allogeneic peripheral blood stem cell transplantation (PBSCT) between 6/14/02 and 6/15/07 at the City of Hope. Indications for the RIC regimen were: (1) aged 50 years or older (42%), (2) compromised organ function (54%), or (3) recipient of a previous HCT (37.5%). Patients had a median age of 47.5 years and the median follow-up was 28.5 months for living patients. Both overall survival (OS) and disease-free survival (DFS) at 2 years was 61.5%. Relapse incidence was 21.1% and nonrelapse mortality (NRM) was 21.5% at 2 years. Chronic graft-versus-host (cGVHD) developed in 86% of evaluable patients. In this series, no significant correlations were made between outcomes and patient age, presence of Philadelphia chromosome, relatedness of donor source, or prior HCT. These high survival rates for high-risk ALL patients following RIC HCT may offer a promising option for patients not eligible for a standard myeloablative transplant.

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**KEY WORDS:** Reduced-intensity, Transplant, ALL, Acute lymphoblastic leukemia

## INTRODUCTION

Acute lymphoblastic leukemia (ALL) has a poor prognosis in adult patients, with a 5-year overall survival (OS) rate of 39% to 50% despite aggressive chemotherapy [1-3], and only 15% for patients over 50 years of age [3]. In patients with high-risk disease, as determined by age, cytogenetics, remission status, and/or response to induction therapy, survival outcomes are even worse [1-3]. According to the MRC/ECOG ALL Trial of chemotherapy versus autologous and allogeneic transplant, allogeneic hematopoietic cell transplantation (HCT) confers the greatest durable benefit for standard-risk adult patients and is more effective than either chemotherapy or autologous transplant [4]. Goldstone et al. [4] also show, however, that for patients over 45 years and others with high-risk ALL, a high nonrelapse mortality (NRM) of 36% offsets any potential survival advantage of the reduced relapse rate conferred by myeloablative (MA) transplant. Patients requiring transplants who are over the age of 50 years, have impaired organ function, or have had previous ablative therapy are unable to withstand the toxicity of the MA protocols that are standard of care.

In the last 10 years, the goal of reducing treatment-related mortality (TRM) has led to the investigation of a variety of reduced-intensity, nonmyeloablative conditioning (RIC, NMA) protocols for allogeneic HCT in patients with multiple hematologic malignancies [5-8]. In a study comparing RIC to standard HCT, NRM (22% versus 30%) and OS (59% versus 52%) were comparable [8]. Similar to observations in the MA transplant setting, Mohty et al. [7] describe a strong

From the [1]Department of Hematology/Hematopoietic Cell Transplantation City of Hope National Medical Center, Duarte, California; [2]Departments of Biostatistics, Pathology, HLA, Blood Bank, City of Hope National Medical Center, Duarte, California; [3]City of Hope–Kaiser Permanente, Los Angeles, California.
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Correspondence and reprint requests: Anthony S. Stein, MD, Department of Hematology & Hematopoietic Cell Transplantation, City of Hope National Medical Center, 1500 E. Duarte Road, Duarte, CA 91010-3000 (e-mail: astein@coh.org).
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association of chronic graft-versus-host disease (cGVHD) with a reduction in relapse incidence from 55% to 30%, suggesting a primary role for graft-versus-leukemia (GVL) in the achievement of remission via RIC HCT.

Four small (22-33 patients) prospective studies [9-12] and a larger (97 patients) retrospective study [13] have attempted to assess the feasibility and effectiveness of RIC specifically for treatment of ALL in high-risk populations. The 2-year OS rates for these studies average 32% (median: 31%, range: 18%-50%), with variable, but high, relapse rates and TRM, depending upon remission status. Consensus conclusions from these studies appear to be that improved survival is associated with RIC transplant during first complete remission (CR1) and that relapse incidence (RI) is lower for patients exhibiting GVHD.

In most published studies of RIC in ALL [9-11,13], multiple sources of hematopoietic stem cells (HSCs) and pretransplant conditioning regimens were included in the same data set, making it difficult to obtain the best and most consistent results. In this study, we have removed the issue of transplantation regimen variation; all patients were treated at the City of Hope with peripheral blood stem cell transplantation (PBSCT) following the same RIC regimen. Based on this more homogeneous treatment and stem cell source, we report a high survival rate among high-risk ALL patients receiving RIC.

## PATIENTS AND METHODS

### Inclusion Criteria

A retrospective analysis was conducted on 24 high-risk ALL patients treated between 6/14/02 and 6/15/07 with a uniform RIC SCT protocol at the City of Hope. The indications for the RIC regimen were 1 or more of the following: (1) patient aged 50 years or older (42%), (2) compromised organ function (54%), or (3) recipient of a previous HCT (37.5%). Indications for HCT during CR1 included age over 35, high white blood cell (WBC) count (>50,000) at diagnosis, multiple rounds of induction chemotherapy required to achieve remission, and/or poor prognosis cytogenetics (e.g., Philadelphia chromosome or t[4;11][q21;q23]). Cytogenetic risk level, based on Pullarkat et al. [14], is indicated in Table 1 as Level 2, 3, 4 or Philadelphia chromosome positive ($Ph^+$) (in increasing order of severity). The City of Hope institutional review board approved the retrospective study and analysis of this patient case series.

### Patients

Salient patient characteristics for all 24 patients are displayed in Table 1. Fifteen women and 9 men were part of the study, with a median age of 47.5 years (range: 23-68 years). Seven patients (29%) had a previous allogeneic HCT and 2 (8%) had a previous autologous HCT. In addition to the high-risk factors for which they were included in this study, the patient population exhibited additional risk factors that could affect outcome: 67% of the PBSC donors were unrelated to the recipients, 54% of patients were beyond CR1 at the time of transplant, and 42% were $Ph^+$. Three patients had ALL that was secondary to a prior malignancy: patient #1 had prior multiple myeloma (MM), #4 breast cancer, and #10 had both a history of chronic lymphocytic leukemia (CLL) and germ cell cancer. One patient, #9, also had a coexisting myelodysplastic syndrome (MDS) at the time of transplant.

Listed first in Table 1 are the 10 patients in CR1 (42%), followed by 1 CR1 patient (#11) who was not in molecular remission (4%), 4 patients in second complete remission (CR2, 17%), 1 induction failure (4%), 3 in first relapse (R1, 12%), 1 in second relapse (R2, 4%), and 4 in third CR or beyond (≥CR3, 17%). For patients in CR1, the median time between remission and transplant was 2.3 months (range: 0.5-5.7), 40% required 2 courses of chemotherapy to achieve remission and the median WBC at diagnosis was 21.5 (range: 0.6-70). Patients not in remission at the time of transplant had a median WBC prior to conditioning of 3.3 (range: 0.9-7.8), a median of 1% blasts in the bone marrow (BM) (range: 0-15), and a median of 0% blasts in the blood (range: 0-21).

Matched sibling donors were available for 8 of the 24 (33%) patients in the study. For the 16 patients lacking suitable related donors, HLA matched unrelated donors (MUDs) were successfully identified through the National Marrow Donor Program (NMDP). HLA typing was performed using polymerase chain reaction (PCR) sequence-specific primers (SSP) or PCR sequence-specific oligonucleotide probe (SSOP) techniques. Of the MUD transplants, mismatches were as follows: 10 patients were matched at 10 of 10 loci, 3 patients had 2 antigen mismatches, 1 patient was allele mismatched, and 1 patient had 2 allele mismatches and an antigen mismatch.

### Treatment Regimen

The RIC regimen for all patients consisted of i.v. Flu at 25 mg/m$^2$ daily for 5 days followed by i.v. melphalan (Mel) at 140 mg/m$^2$ for 1 day. Subsequently, patients received allogeneic PBSC mobilized with granulocyte colony stimulating factor (G-CSF). Eight of the 10 $Ph^+$ patients were treated with thymidine kinase inhibitors (TKI) pre- and/or post-transplant. Table 2 shows details of treatment for $Ph^+$ patients, including type and duration of TKI therapy.

**Table 1. RIC Patient Data**

| Pt No. | Sex | Age at RIC | Compromised Organ Systems | PriorHCT | Status at RIC | Donor Type | GVHD Prophylaxis | Cytogenetic Risk Level* | aGVHD Grade | cGVHD Grade | Outcome dd = death on day rd = relapse on day | Survivor KPS (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 45 | none | Yes | CR1 | MUD | TAC/SIR/MTX | Level 2 | Grade III | Extensive | infection: dd 195 | NA |
| 2 | F | 62 | none | No | CR1 | MUD | CsA/MMF/MTX | Ph+ | None | Extensive | *alive in remission* | 90% |
| 3 | F | 57 | none | No | CR1 | MUD | CsA/MMF/MTX | Ph+ | Grade III | None | infection: dd 245 | NA |
| 4 | F | 57 | none | No | CR1 | SIB | CsA/MMF | Ph+ | Grade II | Extensive | relapsed, rd 857*alive after second RIC* | 90% |
| 5 | F | 56 | renal | No | CR1 | SIB | TAC/SIR | Ph+ | None | Limited | *alive in remission* | 80% |
| 6 | M | 61 | cardiac | No | CR1 | MUD | CsA/MMF/MTX | Ph+ | Grade II | Limited | *alive in remission* | 90% |
| 7 | F | 62 | cardiac, lung | No | CR1 | SIB | TAC/SIR | Unknown | Grade II | Limited | *alive in remission* | 80% |
| 8 | F | 54 | renal, cardiac | No | CR1 | MUD | TAC/SIR/MTX | Level 3 | Grade II | Limited | *alive in remission* | 90% |
| 9 | F | 46 | renal, cardiac | No | CR1 | MUD | TAC/SIR/MTX | Level 2 | Grade II | NA | multiple organ failure: dd 34 | NA |
| 10 | M | 49 | prior chemo/radiation | No | CR1 | MUD | TAC/SIR | Level 3 | Grade I | Limited | *alive in remission* | 100% |
| 11 | M | 38 | none | Yes | CR1† | MUD | CsA/MMF/MTX | Ph+ | Grade IV | NA | idiopathic interstitial pneumonitis: dd 29 | NA |
| 12 | M | 28 | spine irradiation | No | CR2 | MUD | CsA/MMF/MTX | Unknown | Grade I | Extensive | *alive in remission* | Unknown |
| 13 | F | 68 | none | Yes | CR2 | MUD | ATG/CsA/MMF | Ph+ | Grade II | None | disease progression: rd 532, dd 570 | NA |
| 14 | F | 31 | none | Yes | CR2 | SIB | TAC/SIR | Unknown | None | Extensive | disease progression: rd 96, dd 283 | NA |
| 15 | F | 41 | lung | No | CR2 | MUD | TAC/SIR/MTX | Level 2 | Grade III | Extensive | disease progression: rd 207, dd 209 | NA |
| 16 | F | 50 | none | Yes | CR2 | MUD | CsA/MMF/MTX | Level 2 | Grade II | Extensive | *alive in remission* | 90% |
| 17 | F | 54 | pneumonia | No | Induction Failure | SIB | TAC/SIR | Ph+ | Grade I | Extensive | *alive in remission* | 80% |
| 18 | M | 32 | none | Yes | R1 | MUD | CsA/MMF/MTX | Ph+ | None | Extensive | *alive in remission* | 90% |
| 19 | F | 43 | cirrhosis of liver | Yes | R1 | SIB | CsA/MMF | Level 2 | Grade II | Extensive | *alive in remission* | 100% |
| 20 | F | 48 | none | Yes | R1 | MUD | CsA/MMF/MTX | Ph+ | Grade II | Extensive | disease progression: rd 156 ,dd 162 | NA |
| 21 | M | 42 | none | Yes | R2 | MUD | TAC/SIR/MTX | Level 2 | None | None | *alive in remission* | 90% |
| 22 | M | 47 | pneumonia, leukoencephalopathy | No | ≥CR3 | SIB | TAC/SIR | Level 2 | Grade III | NA | leukoencephalopathy dd 53 | NA |
| 23 | M | 23 | cardiac, leukoencephalopathy | No | ≥CR3 | SIB | TAC/SIR | Unknown | None | Extensive | *alive in remission* | 90% |
| 24 | M | 27 | cardiac, lung | No | ≥CR3 | MUD | TAC/SIR/MTX | Level 2 | Grade II | Extensive | *alive in remission* | 90% |

KPS indicates Karnofsky Performance Status score (defined in [18]); CR, complete remission; MUD, matched unrelated donor; TAC, tacrolimus; SIR, sirolimus; MTX, methotrexate; NA, not applicable; CsA, cyclosporine; MMF, mycophenylate mofetil; Ph+, Philadelphia chromosome positive; SIB, sibling donor; ATG, antithymocyte globulin; R, remission; RIC, reduced-intensity conditioning; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease.

*Cytogenetic risk Level defined [14].

†Not in molecular remission.

**Table 2. Ph$^+$ Patient Data**

| Pt No. | Status at RIC | TKI (pre-HCT) | TKI (post-HCT) | Outcome |
|---|---|---|---|---|
| 2 | CR1 | none | none | *alive in remission* |
| 3 | CR1 | imatinib | none | dead, infection |
| 4 | CR1 | imatinib | dasatinib, 4 years | relapsed, second *RIC* |
| 5 | CR1 | imatinib | imatinib, 2.5 years | *alive in remission* |
| 6 | CR1 | imatinib | imatinib, 3 years | *alive in remission* |
| 11 | CR1, mol+ | none | none | dead, IP |
| 13 | CR2 | imatinib | dasatinib, 1 year | dead, progression |
| 17 | Ind failure | imatinib | dasatinib, 2 months | *alive in remission* |
| 18 | R1 | imatinib | imatinib, 5 years | *alive in remission* |
| 20 | R1 | imatinib | imatinib, 2.5 months | dead, progression |

TKI indicates thymidine kinase inhibitor; HCT, hematopoietic cell transplantation; CR, complete remission; mol+, molecular positive; Ind, induction; IP, interstitial pneumonitis; RIC, reduced-intensity conditioning.

The GVHD prophylactic treatment regimen and the maximal extent of acute (aGVHD) and cGVHD manifestations are listed in Table 1 for each patient. Prophylactic treatment of GVHD varied between patients depending on their HLA match and the available protocols at the time of transplant and included: cyclosporine (CsA) plus mycophenylate mofetil (MMF) in 2 patients, CsA/MMF plus methotrexate (MTX) in 8 patients, CsA/MMF plus antithymocyte globulin (ATG) in 1 patient, tacrolimus plus sirolimus in 7 patients, and tacrolimus/sirolimus plus MTX in 6 patients. No patient in this study group was treated using donor leukocyte infusion (DLI).

### Statistics

Survival estimates were calculated based on the product-limit method, and 95% confidence intervals were calculated using the logit transformation and the Greenwood variance estimate [15]. Differences between survival curves were assessed by the log rank test. The significance of demographic/treatment features collected from HCT recipients was assessed using survival analysis and univariate Cox regression analysis [16]. The list of features included was determined from a literature review that identified factors found to be associated with survival and disease relapse in patients treated with allogeneic RIC HCT. Statistical significance was defined at the value of $P \leq .05$.

## RESULTS

### Engraftment

All 24 patients engrafted successfully. The median time, postengraftment, to reach an absolute neutrophil count (ANC) of ≥500, was 15 days (range: 10-26 days), and a platelet count ≥20,000 was 16.5 days (range: 8-24 days). At day 30 postengraftment, short tandem repeat (STR) analysis of BM showed a median of 100% donor cells (range: 90%-100%).

### GVHD

Eighteen patients (75%) developed aGVHD, which was graded according to consensus criteria [17]. Three patients displayed grade I aGVHD, 15 had grade II-IV, with 5 of those suffering grade III or IV. Of the 21 patients evaluable 100 days postengraftment, 18 developed cGVHD (86%); 13 were classified with extensive disease, and 5 with limited cGVHD. Three patients did not develop any symptoms of cGVHD. The 3 patients not evaluable for cGVHD died prior to 100 days postengraftment. We also noted that 9 of the patients had cGVHD with acute features: 4 cases developed progressively from aGVHD, 3 were acute/chronic overlap syndromes, and 2 cases were delayed acute onset (after day100). Only 1 patient exhibited neither aGVHD (grade II or above) nor cGVHD (4%).

### Outcomes

Relapse and death events are reported as days post-HCT and cause of death is listed in Table 1 in the outcome column. Fifteen of the 24 patients were living and disease-free at analysis date, 1 of whom had relapsed (patient #4), but was disease-free 1 year after a second RIC transplant. Karnofsky Performance Status (KPS) scores [18] for survivors are listed in the last column, with all patients at 80% or above and able to carry on relatively normal activity. The KPS score for 1 surviving patient was unobtainable. Of the 13 surviving patients with cGVHD, at the date of analysis, 6 patients had active disease and remained on immunosuppressive therapy, 5 patients had inactive disease and were tapering medications (3 tacrolimus only), and 3 patients were completely off cGVHD medications. Duration of TKI therapy for Ph$^+$ patients is shown in Table 2. TKI therapy was discontinued because of side effects, relapse, or with cessation of immunosuppressive therapy.

Median follow-up for living patients was 28.5 months (range: 12.8-72.5 months). OS and disease-free survival (DFS) at 2 years were both 61.5%, with a confidence interval (CI) of 48.1% to 72.5%. Survival curves for OS and DFS are displayed in Figure 1A and B, respectively. Figure 1B also shows the RI curve, with RI at 14.6% (CI of 5.8%-33.9%) at 1 year and 21.1% (CI of 10.2%-40.7%) at 2 years. NRM was 12.5% (CI of 4.8%-30.2%) at day 100, 21.5% (CI of 11.4%-38.3%) at 1 year and at 2 years, and is charted in Figure 1A. For NRM causes of death in individual patients, see Table 1.

The log rank test was applied to these data to determine whether there were any significant correlations between OS, DFS, RI, or NRM and known variables in the patient population. In contrast to other studies in the literature, at the date of analysis there were no significant relationships found. In particular,

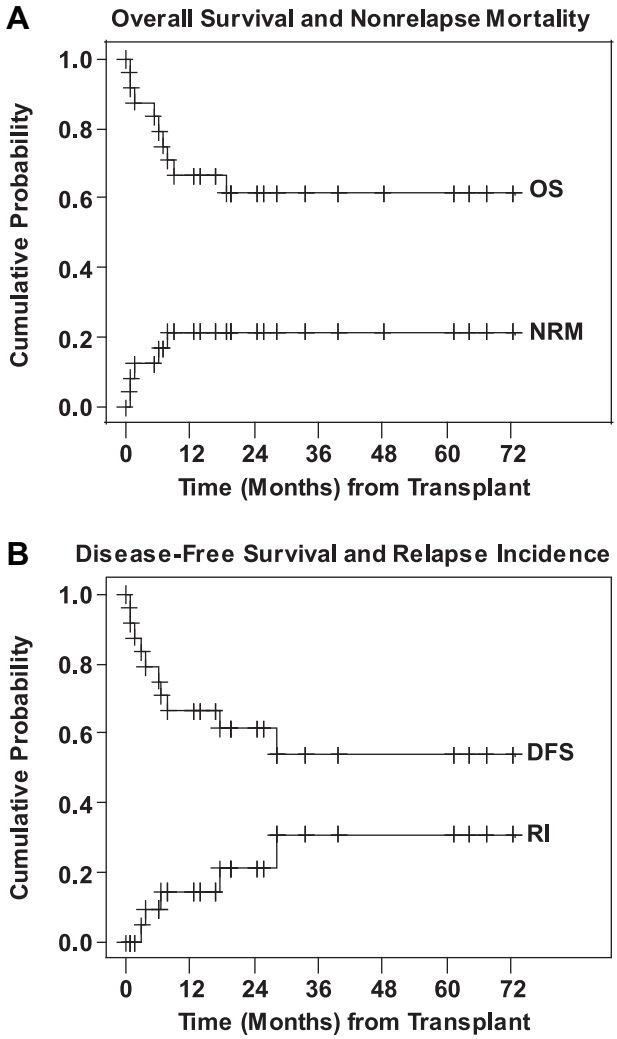


**Figure 1.** RIC outcomes. Median follow-up was 28.5 months (A) OS and NRM, (B) DFS and RI.

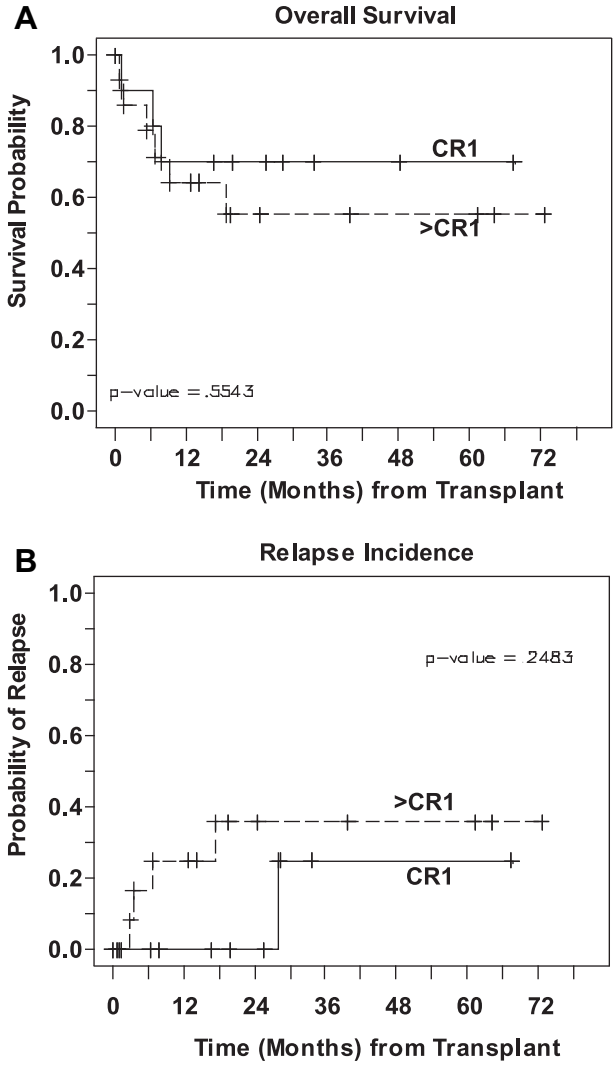


**Figure 2.** CR1 versus >CR1 outcomes. Median follow-up for the 10 CR1 patients was 22.7 months and for the 14 patients at >CR1 was 16.4 months (A) OS and (B) RI.

presence of $Ph^+$ did not affect outcome (60% alive at time of analysis, see Table 2), nor did patient age ≥47 (75% living). Use of an unrelated donor and prior HCT also were not significant factors for outcome with 56% of MUD recipients and 44% of prior HCT recipients alive at the time of analysis. Comparison of patients in CR1 versus those beyond CR1 also yielded no significant differences with respect to outcome and the OS and RI curves are shown in Figure 2. Although some studies have shown a correlation between outcome and the occurrence of cGVHD, no meaningful tests could be performed comparing groups with and without symptoms of cGVHD, as the overwhelming majority of patients exhibited some level of GVHD. Of the 18 patients with cGVHD, 9 had some acute features, either progressive development, overlap syndrome, or delayed acute onset. There was no significant difference in outcomes for the 9 patients with acute features compared to the rest of the population.

## DISCUSSION

ALL is relatively rare in adults and its incidence increases dramatically with age. The cumulative incidence of ALL cases (per 100,000 of age-matched population) triples in the >50 age group compared to the 25-49 age group [19]. Additionally, the older patient population has a higher incidence of $Ph^+$, exemplified by the Southwest Oncology Group (SWOG) study in which the median age is 32 years for the total study group and 47 years for $Ph^+$ patients [14]. Older patients have a very poor prognosis without HCT, but are generally ineligible for MA transplants because of high NRM, as demonstrated in the MRC/ECOG ALL Trial [4]. Goldstone et al. [4] conclude, based on their results in older patients, that research on RIC transplant regimens in ALL is imperative to reduce morbidity and offer a viable alternative to high-risk patients. RIC has the potential to extend the benefit of transplant to those

older patients for whom standard chemotherapy is not effective long term.

Based on the limited ability of DLI to produce a CR in relapsed ALL (only 18% as opposed to 60% for chronic myelogenous leukemia [CML]) [20], some believe that a GVL effect is not clinically important in ALL. Rowe and Goldstone [21] have suggested that the lack of response to DLI may be related to the fact that the DLI study involved patients in active relapse, whereas transplant patients are generally in remission, allowing for a more effective allogeneic response to tumor cells. Several transplant studies do, in fact, suggest that there is a therapeutic GVL effect in ALL, based on a correlation between GVHD and a decrease in relapse incidence among ALL patients, following both MA [22,23] and RIC [7,11] allogeneic HCT. The disparity between DLI-associated and transplant-associated GVL effects may also be because of differences in the ability of ALL blasts to present target antigens, the frequency of minor-antigen reactive T cell precursors, cell cycle kinetics, or susceptibility to lysis [24].

The development of RIC for ALL would give high-risk patients transplant options and hope for disease control with fewer complications. Several studies have attempted to assess the efficacy of RIC for treatment of high-risk ALL; however, most were small and the patient populations and treatment regimens were heterogeneous. In this study at the City of Hope, all patients received a Flu/Mel conditioning regimen and the stem cell source was PBSC. Despite the poor prognostic indicators and limited sample size, the 2-year OS and DFS of 61.5% for this patient population are encouraging. In comparison, the recent MRC/ECOG ALL Trial shows that standard risk ALL patients receiving allogeneic transplants have a 5-year OS of 62%, whereas the Philadelphia chromosome negative ($Ph^-$) high-risk trial patients have an OS of 41% and $Ph^+$ patient OS is only 22% [4].

The 21.5% NRM at 2 years compares very favorably with the International ALL Trial 2-year NRM of 35.8% for high-risk myeloablative transplant patients. The 2-year relapse rate of 21.1% was also similar to the 2-year rate of 25% from the International ALL Trial (interpolated from a 10-year graph) [4]. At 100 days NRM was 12.5%; however, an increase to 21.5% by 2 years posttransplant was attributable to cGVHD and associated infections.

Nearly all patients had GVHD to some extent (23 of 24 patients), and PBSCT is known to correlate with higher risk of GVHD [25]. The incidence of cGVHD was a cause of concern; however, in surviving patients, KPS scores were 80% to 100%, allowing a reasonably functional life after transplant. Jagasia finds that patients having cGVHD with any acute features have a poorer prognosis. In this group, half of the cGVHD cases had some acute features, only 2 of which were delayed acute presentation. There was no correlation between cGVHD with acute features and poor outcome. The low relapse rates in this study may be partially attributable to high GVHD; however, direct statistical tests were inconclusive because of patients numbers.

This study is consistent with the recent findings of Bachanova et al. [12] using CB for ALL RIC, whose 22-patient study is of similar size, high-risk patient composition and outcome. Both studies have a relatively low incidence of relapse (Stein and Forman [24] 2 years: 21%, Bachanova et al. [12] 3 years: 36%), especially for first remission patients after the second year. Although the stem cell sources and treatment details differ, both studies show significant improvement in OS compared to previously published data (Stein and Forman [24] 2 years: 61%, Bachanova et al. [12] 3 year: 50%).

Analysis of this data from 24 high-risk ALL patients did not find a significant association between age and survival; however, that is not unexpected given the skewed age distribution and sample size. Although younger patients might be expected to demonstrate significantly better outcomes in a larger, more age-diverse study, we demonstrate highly acceptable survival rates for older patients receiving RIC. Patients too old to be candidates for MA therapies may now be considered reasonable candidates for RIC PBSCT transplants. In this study, unrelated donor transplant patients had survival rates comparable to patients with related donors. A similar finding for unrelated donors is also recently reported for elderly patients in a large acute myelogenous leukemia (AML) transplant study (368 patients) [26] and in the recent CB ALL study [12]. For older patients, MUD transplant survivability is an important consideration, as the availability of eligible sibling donors diminishes with patient age.

Despite the high-risk nature of the patients in this study, all had low disease burden at the time of transplant, either in a complete remission or with low WBC and % blasts. Forty-two percent of patients were in CR1; however, no significant difference in outcome was detected for these patients compared to those beyond CR1. We are aware that this result is in contrast to the published literature and attribute this to the small sample size.

For adult $Ph^+$ ALL patients, a safer alternative to standard allo-HCT is especially important. Historically, this population had a dismal survival rate of 10% to 20% when treated with standard chemotherapy alone [1,14,27]. Use of imatinib mesylate and other tyrosine-kinase inhibitors is improving remission rates and durable responses, allowing for improved transplant [28] and nontransplant [29] survival. Despite this fact, allo-HCT is considered the only curative approach, and is the standard of care in CR1 for $Ph^+$ ALL patients [27,28,30]. Even though the presence of the Philadelphia chromosome was not part of the selection criteria for RIC in this study, 42% of patients were

$Ph^+$, reflecting the increased incidence of Philadelphia chromosome in older patients. Of the 10 $Ph^+$ patients in this study, 5 have survived in remission, a DFS of 50% that is comparable to the DFS of $Ph^+$ patients seen in a collaborative study by this group and Stanford ($Ph^+$ DFS in CR1 = 48%, beyond CR1 = 26%) [31]. Because of increasing prevalence of $Ph^+$ with increasing age [28,32], the availability of effective reduced-intensity transplants is a crucial addition to the treatment armamentarium for these patients.

In conclusion, this retrospective study demonstrates optimistic survival rates for patients with high-risk ALL undergoing RIC, comparable to those seen in the literature for standard-risk patients undergoing myeloablative allo-HCT. These data also contribute to the body of evidence supporting a role for GVL in the treatment of ALL. Studies describing RIC transplant for ALL are scarce in the literature, and there are as yet no single-protocol prospective trials. Although our findings are exciting, the caveats of the retrospective nature of the study and its small sample size can be addressed only through future prospective trials in adults with ALL. To validate these findings and those of other studies, we plan to use this preliminary data as the basis of a proposal for a large phase II prospective clinical trial of reduced-intensity transplant in patients with high-risk ALL.

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## AUTHORSHIP

Contribution: A.S.S. designed the original study, performed the research, analyzed the data and wrote the paper; J.M.P. and M.L.S. analyzed the data and critically reviewed the paper; N.M.K., R.T.S., N.C.T., K.C.S.W., and D.S. generated data; M.R.D. and D.S.S. critically reviewed the paper; S.H.T. analyzed the data and wrote the paper; and S.J.F. designed the original study and critically reviewed the paper.

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